IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques Dumas et al. Examiner: Chong, Yong Soo

Serial No.: 09/458,014 Group Art Unit: 1617

Filed: December 10, 1999 Confirmation No.: 8328

Title: INHBITION OF P38 KINASE USING ACTIVITY SUBSTITUTED HETEROCYCLIC UREAS

REPLY

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notice of Non-Compliant Amendment dated October 21, 2011, regarding the amendment filed on September 7, 2011, Applicants have resubmitted the amendment showing the deleted text and amended the claims to insert the phrase, "to a patient in need thereof," to claim 1.

The examiner's careful attention to the claim language is appreciated.

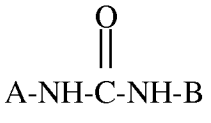
Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

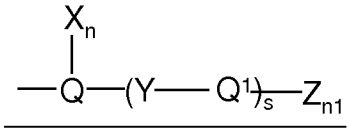
Listing of Claims:

1. (Currently Amended) A method for the treatment of rheumatoid arthritis, comprising administering to a patient in need thereof a compound of formula I



I

wherein B is



wherein Y is selected from the group consisting of –O-, -S-, -CH_2-, -SCH_2-, -CH_2S-, -CH(OH)-, -C(O)-, -CX^a_2, -CX^aH-, -CH_2O- and -OCH_2-, where X^a is halogen,

Q is a six member aromatic structure containing 0–2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution;

Q^1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution, and

~~wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n;~~

wherein n is 0-2~~3~~ and each X is independently selected from the group consisting of –CN, -CO_2R^5, -C(O)$NR^5R^{5'}$, -C(O)R^5, -NO_2, -OR^5, - SR^5, - $NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl,

substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

~~wherein Y is –O–, –S–, $-N(R^5)-$, $-(CH_2)_m-$, –C(O)–, –CH(OH)–, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-NR^5C(O)NR^5R^{5'}-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,~~

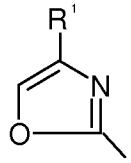
~~m = 1-3, and X^a is halogen~~; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1},

wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, -C(O)- NR^5, $-NO_2$, =O, $-OR^5$, - SR^5, - $NR^5R^{5'}$, $-C(O)R^5$, $-SO_2R^5$, $-SO_2NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^{5'}$,$-C(O)NR^5R^{5'}$, =O, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C-C_{10} heteroaryl, C_6-C_{14} aryl, C_4-C_{24} alkheteroaryl and C_7-C_{24} alkaryl

A is a heteroaryl moiety selected from the group consisting of



wherein

R^1 is selected from the group consisting of halogen, C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl.

2.-3. (Cancelled)

4. (Currently Amended) A method as in claim 1~~3~~, wherein

Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution,

Q^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, or -Y-Q^1 is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution, and

Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

5-7. (Cancelled)

8. (Previously Presented) A method as in claim 1, wherein R^1 is t-butyl.

9-27. (Cancelled)

28. (Previously Presented) A method as in claim 1, wherein the compound for formula

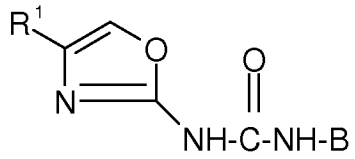
I displays p38 IC_{50}'s of less than 10 μm as determined by an in-vitro p38 kinase inhibition assay.

29. (Cancelled)

30. (Previously Presented) A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit p38.

31-37. (Cancelled)

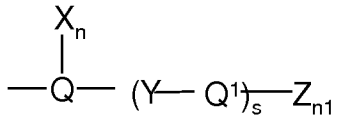
38. (Currently Amended) A method as in claim 1 comprising administering a compound of the
formula



wherein R^1 is t-butyl and B ~~are~~is as defined in claim 1.

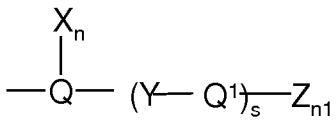
39-43. (Cancelled)

44. (Previously Presented) A method as in claim 1, wherein B is of the formula



wherein Q is phenyl or pyridinyl, optionally substituted by halogen up to per-halosubstitution, Q^1 is pyridinyl, phenyl or benzothiazolyl optionally substituted by halogen up to per-halosubstitution, Y is –O-, -S-, $-CH_2S-$, $-SCH_2-$, $-CH_2O-$, $-OCH_2-$ or $–CH_2-$, X is C_1-C_4 alkyl or up to per-halosubstituted C_1-C_4 alkyl and Z is as defined in claim 1 , n = 0 or 1, s = 1 and n1 = 0-1.

45. (Previously Presented) A method as in claim 38, wherein B is of the formula



Q is phenyl or pyridinyl, optionally substituted by halogen up to per-halosubstitution, Q^1 is pyridinyl, phenyl or benzothiazolyl optionally substituted by halogen up to per-halosubstitution, Y is –O-, -S-, -C(O)- or $–CH_2$-, X is C_1-C_4 alkyl or up to per-halosubstituted C_1-C_4 alkyl and Z is as defined in claim 1 n = 0 or 1, s = 0 or 1 and n1 = 0 or 1.

46-49. (Cancelled)

50. (Previously Presented) A method as in claim 1, wherein B is

a) phenyl, pyridinyl, naphthyl, quinolinyl or isoquinolinyl, substituted by -Y-Ar and optionally substituted by

-halogen up to per-halosubstitution,

-C_1-C_4 alkyl,

-up to per-halosubstituted C_1-C_4 alkyl, or

- a combination thereof,

wherein Y and Ar are as defined in claim 1;

b) thienyl substituted by methyl; or

c) indolyl substituted by phenyl or pyridyl.

51. (Previously Presented) A method as in claim 1, wherein B is phenyl or pyridinyl substituted by -Y-Ar and optionally substituted by

-halogen ,up to per-halosubstitution,

-C_1-C_4 alkyl,

-up to per-halosubstituted C_1-C_4 alkyl, or

- a combination thereof,

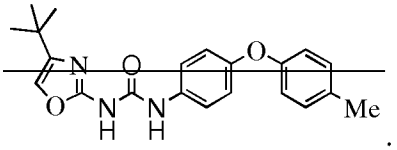
wherein Y and Ar are as defined in claim 1.

52-54. (Cancelled)

55. (Previously Presented) A method according to claim 1, wherein R^1 is selected from the group consisting of halogen, C_3-C_{10} cycloalkyl, C_1-C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl.

56-57. (Cancelled)

58. (Currently Amended) A method for the treatment of rheumatoid arthritis comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound of formula I in claim 1.



REMARKS

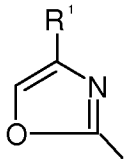
Applicants thank the Examiner for conducting a telephonic interview to clarify the requirements of the Ex parte Quayle action. Applicants maintain that with the exception of canceling claim 53, no amendments to the claims are necessary. However, the claims have been amended toward the subject matter that the Examiner indicated was preferred in the interview.

Claim Amendments and the Restriction Requirement

Applicants have canceled claim 53 as requested by the Office Action.

The Office Action requires the claims to reflect the elected subject matter as a result of Restriction Requirements in the current application, i.e. that the claims be drawn to a method of treating rheumatoid arthritis by administering a 1,3 oxazole according to compounds of formula 1 classified in 514/385. Applicants respectfully submit that the claims reflect such an election.

The independent claim states, "A method for the treatment of rheumatoid arthritis," and also "A is a heteroaryl moiety selected from the group consisting of



." See claim 1. Applicants have also amended claim 1 to include the limitations of claim 3. Applicants respectfully submit that sections 1 and 2 of the Ex parte Quayle action have been satisfied.

Requirement for a Terminal Disclaimer

Applicants respectfully submit that a terminal disclaimer is unessacary. The only patent cited in the Office Action is US Pat. No. 7,838,541, which does not claim either the treatment of rheumatoid arthritis or administering 1, 3 oxazole according to compounds of formula I of the claims of the current application. US Pat. No. 7,838,541 is directed toward treating retinopathy and retinopathy of prematurity using compounds of a formula I without 1, 3 oxazole.

MPEP 804 1(b) which states, "If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should

withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

All of the patent applications cited in the office Action have a filing date on or after the filing date of the current application. Therefore, in accordance with MPEP 804 1(b) the current application should be allowed to issue without a terminal disclaimer.

In view of the above arguments applicants respectfully request that the Ex parte Quayle action be withdrawn and the application be allowed to issue.

Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Ryan Pool/

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